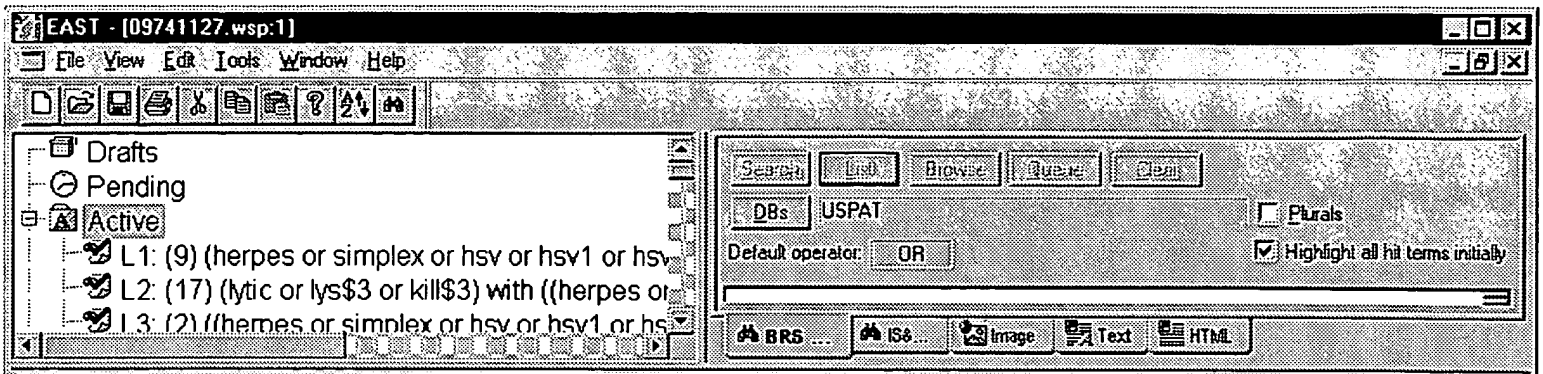

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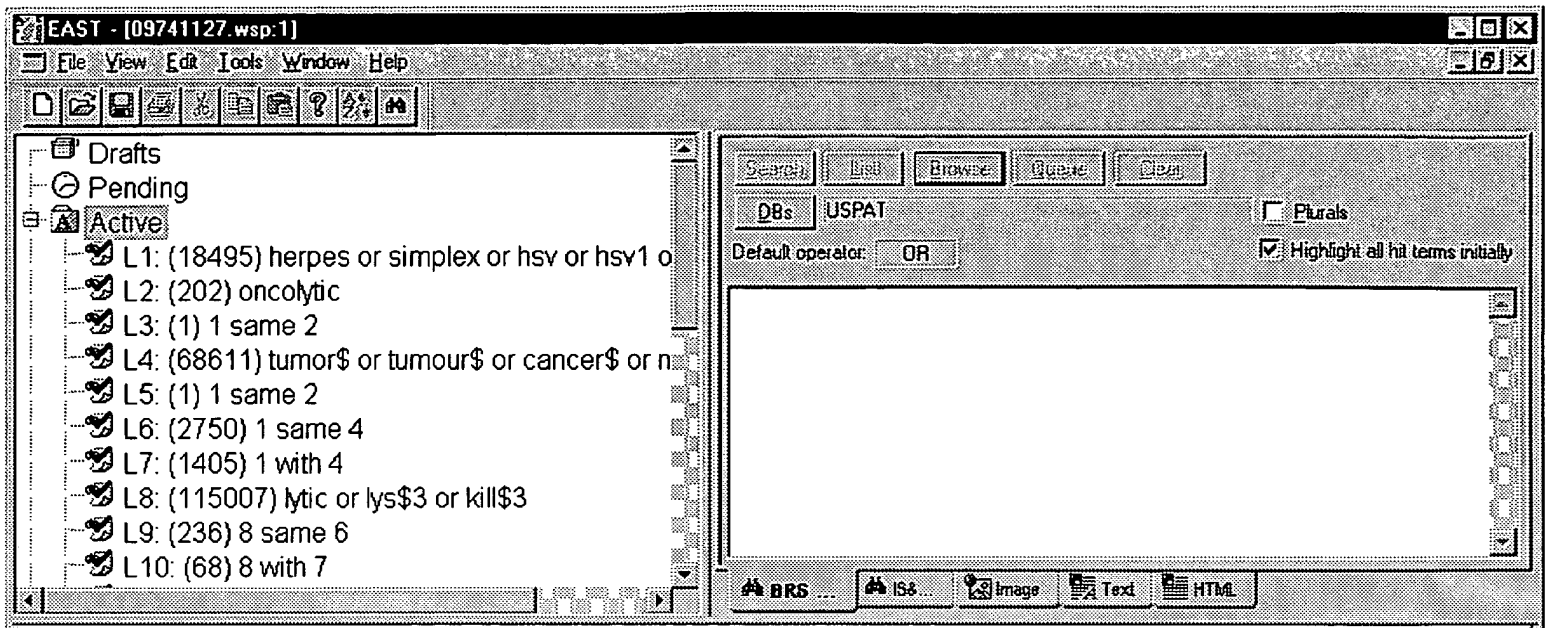
5	BRS	L5	1	((treat$6 or therap$6) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) same (gc or glycoprotein adj c or ul44)	US-PGPUB	2002/07/17 08:21
6	BRS	L7	147	(lytic or lys$3 or kill$3) and ((herpes or simplex or hsv or hsv1 or hsv2) and (tumor$ or tumour$ or cancer$ or neoplas$))	EPO; JPO; DERWENT	2002/07/17 08:19
7	BRS	L6	9	(herpes or simplex or hsv or hsv1 or hsv2) and oncolytic	EPO; JPO; DERWENT	2002/07/17 08:21
8	BRS	FAMILY	1	2001-381907.NRAN.	DERWENT	2002/07/17 08:22
9	BRS	L8	67	(lytic or lys$3 or kill$3) same ((herpes or simplex or hsv or hsv1 or hsv2) same (tumor$ or tumour$ or cancer$ or neoplas$))	EPO; JPO; DERWENT	2002/07/17 08:24
10	BRS	L9	10	((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44)) with (mutat$4 or mutant$1 or delet$4 or insert$4)	EPO; JPO; DERWENT	2002/07/17 08:25
11	BRS	L10	12	((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44)) same (mutat$4 or mutant$1 or delet$4 or insert$4)	EPO; JPO; DERWENT	2002/07/17 08:26
12	BRS	L11	0	((lytic or lys$3 or kill$3) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) and (((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44))	EPO; JPO; DERWENT	2002/07/17 08:26
13	BRS	L12	1	((treat$6 or therap$6) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) same (gc or glycoprotein adj c or ul44)	EPO; JPO; DERWENT	2002/07/17 08:26



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5	BRS	L5	1	1 same 2	USPAT	2002/07/17 07:45
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8	BRS	L8	115007	lytic or lys$3 or kill$3	USPAT	2002/07/17 07:46
9	BRS	L9	236	8 same 6	USPAT	2002/07/17 07:46
10	BRS	L10	68	8 with 7	USPAT	2002/07/17 08:03
11	BRS	L11	26708	gc or glycoprotein adj c or ul44	USPAT	2002/07/17 07:54
12	BRS	L12	222	1 with 11	USPAT	2002/07/17 07:52
13	BRS	L13	970543	mutat$4 or mutant$1 or delet$4 or insert$4	USPAT	2002/07/17 07:52
14	BRS	L14	55	12 with 13	USPAT	2002/07/17 07:53
15	BRS	L15	1	10 and 14	USPAT	2002/07/17 08:03
16	BRS	L16	748448	treat$6 or therap$6	USPAT	2002/07/17 08:07
17	BRS	L17	1519	16 same 6	USPAT	2002/07/17 08:07
18	BRS	L18	557	16 with 7	USPAT	2002/07/17 08:07
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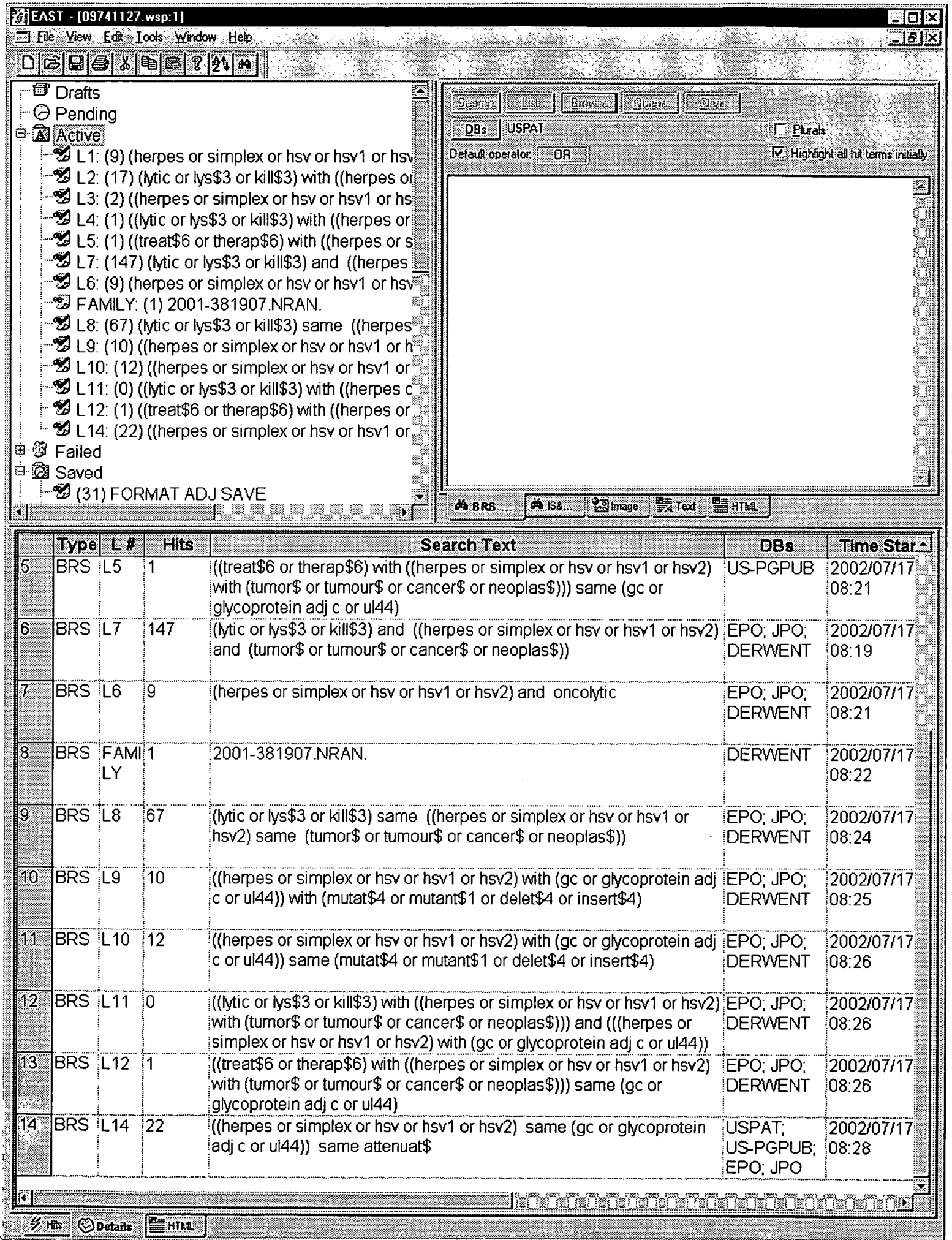
20	BRS	L19	78	18 and 11	USPAT	2002/07/17 08:08



	Type	L #	Hits	Search Text	DBs	Time Star
5	BRS	L5	1	((treat$6 or therap$6) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) same (gc or glycoprotein adj c or ul44)	US-PGPUB	2002/07/17 08:21
6	BRS	L7	147	(lytic or lys$3 or kill$3) and ((herpes or simplex or hsv or hsv1 or hsv2) and (tumor$ or tumour$ or cancer$ or neoplas$))	EPO; JPO; DERWENT	2002/07/17 08:19
7	BRS	L6	9	(herpes or simplex or hsv or hsv1 or hsv2) and oncolytic	EPO; JPO; DERWENT	2002/07/17 08:21
8	BRS	FAMILY	1	2001-381907.NRAN.	DERWENT	2002/07/17 08:22
9	BRS	L8	67	(lytic or lys$3 or kill$3) same ((herpes or simplex or hsv or hsv1 or hsv2) same (tumor$ or tumour$ or cancer$ or neoplas$))	EPO; JPO; DERWENT	2002/07/17 08:24
10	BRS	L9	10	((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44)) with (mutat$4 or mutant$1 or delet$4 or insert$4)	EPO; JPO; DERWENT	2002/07/17 08:25
11	BRS	L10	12	((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44)) same (mutat$4 or mutant$1 or delet$4 or insert$4)	EPO; JPO; DERWENT	2002/07/17 08:26
12	BRS	L11	0	((lytic or lys$3 or kill$3) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) and (((herpes or simplex or hsv or hsv1 or hsv2) with (gc or glycoprotein adj c or ul44))	EPO; JPO; DERWENT	2002/07/17 08:26
13	BRS	L12	1	((treat$6 or therap$6) with ((herpes or simplex or hsv or hsv1 or hsv2) with (tumor$ or tumour$ or cancer$ or neoplas$))) same (gc or glycoprotein adj c or ul44)	EPO; JPO; DERWENT	2002/07/17 08:26
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(25) Filing Language: English

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(74) Agent: GIOTTA, Gregory; Onyx Pharmaceuticals, Inc., 3031 Research Drive, Richmond, CA 94806 (US).

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(54) Title: HERPES SIMPLEX VIRUS-1 GLYCOPROTEIN C MUTANTS FOR TREATING UNWANTED HYPERPROLIFERATIVE CELL GROWTH

(57) Abstract: The present invention relates to pharmaceutical compositions, kits, and methods of use thereof, comprising, a mutant human herpes simplex virus, which is cytopathic to susceptible target cells, such as neoplastic cells. Preferably, the virus does not produce a functionally active wild-type gC polypeptide coded for the UL44 gene.

? b 155,357
17jul02 07:32:38 User208669 Session D2059.1
$0.32 0.090 DialUnits File1
$0.32 Estimated cost File1
$0.01 TELNET
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$0.33 Estimated total session cost 0.090 DialUnits

SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1966-2002/Jul W2
File 357:Derwent Biotech Res. 1982-2002/June W1
(c) 2002 Thomson Derwent & ISI
*File 357: Price changes as of 1/1/02. Please see HELP RATES 357.
Derwent announces file enhancements. Please see HELP NEWS 357.

Set Items Description
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Set Items Description
S1 31204 SIMPLEX OR HSV?
S2 22365 GC OR GLYCO?(W) C OR UL44 OR UL(W)44
S3 619 S1 AND S2
S4 85998 ATTENUAT?
S5 11 S3 AND S4
S6 0 VIRULEN$
S7 34832 VIRULEN?
S8 23 S7 AND S3 NOT S5
S9 88514 COMPLEMENT
S10 1415023 TUMOR? OR TUMOUR? OR NEOPLAS? OR CANCER? OR CARCINO?
S11 9375 S9 AND S10
S12 610 ONCOLYSIS? OR ONCOLYTIC?
S13 19 S9 AND S12
S14 312280 KILL? OR DEATH
S15 1055 S14 AND S10 AND S9
S16 461735 VIRUS OR VIRAL OR VIRUSES
S17 123 S16 AND S15
S18 3030483 TREAT? OR THERAP?
S19 57 S17 AND S18
S20 6183 S9 (2N) (MEDIAT? OR DEPEND?)
S21 254 S15 AND S20
S22 23 S16 AND S21
S23 23 RD (unique items)
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5/7/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10705845 20236013 PMID: 10774198
[The relationship between gene function and virulence in alpha-herpesviruses]
Suzutani T
Department of Microbiology, Asahikawa Medical College.
Nippon rinsho. Japanese journal of clinical medicine (JAPAN) Apr 2000, 58 (4) p801-6, ISSN 0047-1852 Journal Code: 0420546
Document type: Journal Article; Review; Review Literature ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed
Virulent alpha-herpesvirus genes, though not essential for virus replication in cell culture, play important roles in virus replication in vivo. In this paper, I classify the virulent genes and discuss the relationship between gene function and virulence. The products of the virulent genes of herpes simplex virus, described in this paper, are enzymes (thymidine kinase, ribonucleotide reductase, deoxyuridine triphosphatase, DNA polymerase, and two protein kinases), glycoproteins (gC, gE), immediate early gene product (ICP47) and gamma 34.5. To identify the virulent genes of varicellazoster virus, mutation in the Oka vaccine strain was studied. The low levels of gV expression and mutation found in the immediate early gene were predicted as the cause of the attenuation of the Oka vaccine strain. (27 Refs.)
Record Date Created: 20000706

5/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10521784 20054504 PMID: 10587354
In vivo role of complement-interacting domains of herpes simplex virus type 1 glycoprotein gC.
Lubinski J; Wang L; Mastellos D; Sahu A; Lambris J D; Friedman H M
Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
Journal of experimental medicine (UNITED STATES) Dec 6 1999, 190 (11) p1637-46, ISSN 0022-1007 Journal Code: 2985109R
Contract/Grant No.: RO1 HL 28220; HL; NHLBI
Erratum in J Exp Med 2000 Feb 21;191(4) following 746
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Immune evasion is critical for survival of viruses that establish persistent or recurrent infections. However, at the molecular level, little is known about how viruses evade immune attack in vivo. Herpes simplex virus (HSV)-1 glycoprotein gC has two domains that are involved in modulating complement activation; one binds C3, and the other is required for blocking C5 and properdin (P) binding to C3. To evaluate the importance

of these regions in vivo, HSV-1 gC mutant viruses were constructed that lacked one or both gC domains and studied in a murine model of infection. Each gC region of complement regulation contributed to virulence; however, the C3 binding domain was far more important, as virus lacking this domain was much less virulent than virus lacking the C5/P inhibitory domain and was as attenuated as virus lacking both domains. Studies in C3 knockout mice and mice reconstituted with C3 confirmed that the gC domains are inhibitors of complement activation, accounting for a 50-fold difference in virulence between mutant and wild-type viruses. We conclude that the C3 binding domain on gC is a major contributor to immune evasion and that this site explains at a molecular level why wild-type virus resists complement attack.

Record Date Created: 20000113

5/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09681919 98105734 PMID: 9444989

Attenuation of the vaccine Oka strain of varicella-zoster virus and role of glycoprotein C in alphaherpesvirus virulence demonstrated in the SCID-hu mouse.

Moffat J F; Zerboni L; Kinchington P R; Grose C; Kaneshima H; Arvin A M

Department of Pediatrics, Stanford University School of Medicine, California 94305-5208, USA.

Journal of virology (UNITED STATES) Feb 1998, 72 (2) p965-74, ISSN 0022-538X Journal Code: 0113724

Contract/Grant No.: AI09195; AI; NIAID; AI20459; AI; NIAID; HD07249; HD; NICHD; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The SCID-hu mouse implanted with human fetal tissue is a novel model for investigating human viral pathogenesis. Infection of human skin implants was used to investigate the basis for the clinical attenuation of the varicella-zoster virus (VZV) strain, V-Oka, from which the newly licensed vaccine is made. The pathogenicity of V-Oka was compared with that of its parent, P-Oka, another low-passage clinical isolate, strain Schenke (VZV-S), and VZV-Ellen, a standard laboratory strain. The role of glycoprotein C (gC) in infectivity for human skin was assessed by using gC-negative mutants of V-Oka and VZV-Ellen. Whereas all of these VZV strains replicated well in tissue culture, only low-passage clinical isolates were fully virulent in skin, as shown by infectious virus yields and analysis of implant tissues for VZV DNA and viral protein synthesis. The infectivity of V-Oka in skin was impaired compared to that of P-Oka, providing the first evidence of a virologic basis for the clinical attenuation of V-Oka. The infectivity of V-Oka was further diminished in the absence of gC expression. All strains except gC-Ellen retained some capacity to replicate in human skin, but cell-free virus was recovered only from implants infected with P-Oka or VZV-S. Although VZV is closely related to herpes simplex virus type 1 (HSV-1) genetically, experiments in the SCID-hu model revealed differences in tropism for human cells that correlated with differences in VZV and HSV-1 disease. VZV caused extensive infection of epidermal and dermal skin cells, while HSV-1 produced small, superficial lesions restricted to the epidermis. As in VZV, gC expression was a determinant for viral replication in skin. VZV infects human CD4+ and CD8+ T cells in thymus/liver implants, but HSV-1 was detected only in epithelial cells, with no evidence of lymphotropism. These SCID-hu mouse experiments show that the clinical attenuation of the varicella vaccine can be attributed to decreased replication of V-Oka in skin and that tissue culture passage alone reduces the ability of VZV to infect human skin in vivo. Furthermore, gC, which is dispensable for replication in tissue culture, plays a critical role in the virulence of the human alphaherpesviruses VZV and HSV-1 for human skin.

Record Date Created: 19980218

5/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
07288326 92223157 PMID: 1314100

In vivo expression of beta-galactosidase in hippocampal neurons by HSV-mediated gene transfer.

Fink D J; Sternberg L R; Weber P C; Mata M; Goins W F; Glorioso J C

Department of Neurology, University of Michigan, Ann Arbor 48105.

Human gene therapy (UNITED STATES) Feb 1992, 3 (1) p11-9, ISSN 1043-0342 Journal Code: 9008950

Contract/Grant No.: GM34534; GM; NIGMS; NF 27771; NF; NSF

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Stereotactic inoculation of a herpes simplex virus (HSV) gene transfer vector into the hippocampus and caudate of rat brain resulted in limited and transient viral replication and the establishment of latency. Virus attenuation was achieved by insertional inactivation of a viral gene, Us3. Insertion of a lacZ reporter gene, under the control of the HSV glycoprotein C (gC) late gene promoter, allowed viral replication to be monitored in vivo. Unlike unattenuated virus, the Us3::pgC-lacZ recombinant caused little apparent damage to normal hippocampal morphology. Transient lacZ expression was detected in a considerable population of neurons of the dentate gyrus following hippocampal injection, whereas few positively staining neurons were present within the caudate after injection at that site. Latency-associated transcripts, the hallmark of latent infection, were detected in the brain 10 months after injection. This recombinant virus may be useful as a gene transfer vector for long-term expression of foreign genes in the central nervous system.

Record Date Created: 19920521

5/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
05448641 87201150 PMID: 2437431
Mechanism of differences in pathogenicity between two variants of a laboratory strain of herpes simplex virus type 1.
Yamada M; Arao Y; Uno F; Nii S
Microbiology and immunology (JAPAN) 1986, 30 (12) p1259-70, ISSN 0385-5600 Journal Code: 7703966
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mechanisms responsible for the difference in neurovirulence to inbred mice between two variants of the Miyama strain of herpes simplex virus type 1 (HSV-1) were studied. After intraperitoneal (i.p.) inoculation, the +GC (LPV) variant reached the spinal cord and the brain, and caused death. Conversely, the -GCr variant lacked the ability to gain access to the central nervous system (CNS) after the same route of infection and failed to kill susceptible mice. The initial virus growth after i.p. inoculation, as indicated by the number of infective centers (ICs) produced by the peritoneal exudate cells (PECs), was compared between these two variants. The virulent +GC (LPV) strain induced much more ICs than the attenuated -GCr variant. When the attenuated variant was preinoculated i.p. 24 hr before the challenge inoculation with the virulent variant by the same route, the production of ICs by the pathogenic variant was highly inhibited, and growth of this variant did not occur in the CNS. Thus, mice were protected from lethal infection by the virulent variant by preinoculation with the attenuated one. Moreover, the ability of mice to resist i.p. infection by HSV-1 was shown to be age-dependent.
Record Date Created: 19870527

5/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
03015063 79087882 PMID: 215551
Suppression of in vitro growth of virulent and avirulent herpes simplex viruses by cell-mediated immune mechanisms, antibody, and interferon.
Shimizu F; Satoh J; Tada M; Kumagai K
Infection and immunity (UNITED STATES) Dec 1978, 22 (3) p752-7, ISSN 0019-9567 Journal Code: 0246127
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A rounding cell-forming--GC strain, which is a variant of a syncytial giant cell-forming herpes simplex virus (+GC Miyama strain), was highly attenuated for Swiss, BALB/c nu/nu, and nu/+ mice, whereas +GC was highly virulent to all the mice tested. +GC and -GC were antigenically indistinguishable from each other by cross-neutralization and cross-immunization. Immunosuppression induced by cyclophosphamide converted the nonlethal -GC infection of mice into a fatal infection. -GC replication in tissue culture was more effectively suppressed by spleen cells immunized with either +GC or -GC than was the +GC replication. -GC replication was also inhibited more effectively by antibody or the antibody-dependent cell-mediated system than was the +GC replication. -GC is highly sensitive to mouse interferon, but +GC was relatively resistant. These findings indicate that attenuation of this avirulent -GC strain may be due to a high susceptibility of its replication to humoral and cell-mediated defense factors. The probable roles of each defense factor in recovery from the infection with virulent and attenuated herpes simplex virus are also discussed.
Record Date Created: 19790328
? t s8/7/5-7 9 11 12-14 16 18-21 23
8/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09956640 98406233 PMID: 9733869
Herpes simplex virus type 1 glycoprotein gC mediates immune evasion in vivo.
Lubinski J M; Wang L; Soulika A M; Burger R; Wetsel R A; Colten H; Cohen G H; Eisenberg R J; Lambris J D; Friedman H M
Departments of Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
Journal of virology (UNITED STATES) Oct 1998, 72 (10) p8257-63, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: AI 25011; AI; NIAID; HL 28220; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Many microorganisms encode proteins that interact with molecules involved in host immunity; however, few of these molecules have been proven to promote immune evasion in vivo. Herpes simplex virus type 1 (HSV-1) glycoprotein C (gC) binds complement component C3 and inhibits complement-mediated virus neutralization and lysis of infected cells in vitro. To investigate the importance of the interaction between gC and C3 in vivo, we studied the virulence of a gC-null strain in complement-intact and C3-deficient animals. Using a vaginal infection model in complement-intact guinea pigs, we showed that gC-null virus grows to lower titers and produces less severe vaginitis than wild-type or gC rescued virus, indicating a role for gC in virulence. To determine the importance of complement, studies were performed with C3-deficient guinea pigs; the results demonstrated significant increases in vaginal titers of gC-null virus, while wild-type and gC rescued viruses showed nonsignificant changes

in titers. Similar findings were observed for mice where gC null virus produced significantly less disease than gC rescued virus at the skin inoculation site. Proof that C3 is important was provided by studies of C3 knockout mice, where disease scores of gC-null virus were significantly higher than in complement-intact mice. The results indicate that gC-null virus is approximately 100-fold (2 log10) less virulent that wild-type virus in animals and that gC-C3 interactions are involved in pathogenesis.
Record Date Created: 19981007

8/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09795067 98227931 PMID: 9568976
Glycoprotein C-deficient mutants of two strains of herpes simplex virus type 1 exhibit unaltered adsorption characteristics on polarized or non-polarized cells.
Griffiths A; Renfrey S; Minson T
Department of Pathology, University of Cambridge, UK.
Journal of general virology (ENGLAND) Apr 1998, 79 (Pt 4) p807-12, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Mutants of herpes simplex virus type 1 (HSV-1) strain SC16, lacking each of the dispensable glycoproteins C, G, E, I or J, were examined for their ability to infect the apical or basolateral surfaces of polarized human epithelial cells. None of the mutants was significantly different from the wild-type parent when assayed on either surface. Since a previous report had demonstrated that glycoprotein C (gC) was necessary for the infection of apical surfaces of polarized epithelium, a second gC-negative mutant was constructed on a background of HSV-1 strain HFEM. This mutant displayed no phenotype when assayed on the apical surface. Furthermore, neither gC-negative mutant differed from its wild-type parent in its adsorption kinetics or specific infectivity on non-polarized Vero cells, a result which is inconsistent with the view that interactions between gC and cell surface proteoglycans constitute the initial adsorption process. Our findings thus conflict with previous reports and suggest that proposed functions of HSV-1 gC in the infection of polarized and non-polarized cells may be strain-dependent.
Record Date Created: 19980512

8/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09515030 97417327 PMID: 9272700
Pathogenicity of glycoprotein C-deficient herpes simplex virus 1 strain TN-1 which encodes truncated glycoprotein C.
Minagawa H; Liu Y; Yoshida T; Hidaka Y; Toh Y; Mori R
Department of Virology, Faculty of Medicine, Kyushu University, Fukuoka, Japan. hmina@virology.med.kyushu-u.ac.jp
Microbiology and immunology (JAPAN) 1997, 41 (7) p545-51, ISSN 0385-5600 Journal Code: 7703966
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A clinical isolate of herpes simplex virus 1 (TN-1) from a stromal keratitis patient was found to be defective in the glycoprotein C (gC) gene (UL44), thus resulting in the production of truncated gC upon infection. To study the pathogenetic role of truncated gC, we prepared a recombinant LTN-8 derived from TN-1 with deletions of the 1.5 kilobase pairs of the gC gene including the initiation codon. A penetration assay revealed LTN-8 to be less efficient in its penetration ability than TN-1, the laboratory strain KOS and RTN-1-20-3, a recombinant derived from TN-1 with the KOS gC gene. The penetration of LTN-8 was facilitated by the addition of TN-1-infected culture medium. TN-1 virus preparations had no hemagglutinating activity. However, the animals infected with TN-1 did develop hemagglutination inhibition (HI) antibodies. The LTN-8-infected animals did not develop HI antibodies. The pathogenicity in BALB/c mice following either corneal, intraperitoneal or intracerebral inoculation did not significantly differ among TN-1, RTN-1-20-3 or LTN-8. Our results indicate that truncated gC was sufficient for the induction of HI antibodies and was also able to facilitate penetration in vitro. Although truncated gC might be a virulence factor acting as a decoy, both truncated gC and intact gC had little effect on the outcome following intracerebral, intraperitoneal or corneal inoculation.
Record Date Created: 19971006

8/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
08961295 96312988 PMID: 8708138
Highly virulent strains of herpes simplex virus fail to kill mice following infection via gingival route.
Monma Y; Chen Z J; Mayama H; Kamiyama K; Shimizu F
Department of Pediatric Dentistry, Tohoku University School of Dentistry, Sendai, Japan.
Journal of dental research (UNITED STATES) Apr 1996, 75 (4) p974-9, ISSN 0022-0345 Journal Code: 0354343
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Virulence of herpes simplex virus (HSV) in mice has been demonstrated to be dependent on the site of infection. In this experiment, pathogenesis of HSV was studied in 2 different routes of infection in a mouse model system.

When BALB/c mice were infected with 5 x 10(3) plaque-forming units (PFU) of virulent HSV type 1 Miyama GC+ strain (HSV-1-GC+) intraperitoneally, all mice were dead in 6 to 9 days. HSV-1-GC+ was recovered from organs such as the cerebrum, cerebellum, brainstem, and spleen 2 to 5 days after infection, but not from other organs such as trigeminal ganglia. However, if mice were infected in the maxillary gingiva with 1.0 x 10(7) PFU of HSV-1-GC+, all mice survived. HSV-1-GC+ was recovered from the trigeminal ganglia and brainstem 2 to 5 days after infection, but not from other organs tested. When mice were infected in maxillary gingiva with HSV-1-GC+, followed by the intraperitoneal injection of 6 mg of cyclophosphamide 72 hrs after virus infection, all mice were dead within days. Immunofluorescent and hematoxylin-eosin staining of gingival tissue sections revealed that when mice were infected in maxillary gingiva with HSV-1-GC+, 3 times as many gamma delta T-cells and 5 times as many polymorphonuclear cells can be detected in sections of maxillary gingiva when compared with non-infected mice. These data show that the gingiva of mice is considerably more resistant to infection with HSV, compared with the peritoneal cavity, and suggest the possible presence of an oral defense mechanism which might be different from that in the peritoneal cavity.
Record Date Created: 19960910

8/7/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
07255271 92186891 PMID: 1312221
Mapping neuroinvasiveness of the herpes simplex virus type 1 encephalitis-inducing strain 2762 by the use of monoclonal antibodies.
Bergstrom T; Sjogren-Jansson E; Jeansson S; Lycke E
Department of Clinical Virology, University of Goteborg, Sweden.
Molecular and cellular probes (ENGLAND) Feb 1992, 6 (1) p41-9, ISSN 0890-8508 Journal Code: 8709751
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Monoclonal antibodies (MAbs) directed against herpes simplex virus (HSV)-coded glycoproteins gB, gC, gD and gE were employed in a an in vitro model of neuroinvasiveness using sensory neurons from rat dorsal root ganglion (DRG) cells. The neurons were cultured in at two-chamber system allowing infection via the neuritic extensions exclusively. The effects of 30 MAbs on viral replication of the encephalitis-derived HSV-1 strain 2762 and its less neuroinvasive variant 2762p11 were assayed in this model. One MAb reactive with gD gave a nine-fold reduction of the virus yields of both strains. One MAb directed against gB gave an enhanced virus yield of strain 2762, but not of the 2762p11 variant. Another gB-reactive MAb decreased the virus yield of strain 2762p11, but not of 2762 after neuritic infection. The findings indicate that an alteration of gB has occurred during the passage of the strain 2762. Mutants of the same strain were derived by infecting hybridomas producing MAb reactive with gB, gC, gD and gE, respectively. The gB hybridoma mutant showed a significantly lower neuroinvasiveness in the DRG model, and was non-virulent after snout infection of mice. We suggest that the structure of gB of the strain 2762 is of importance for the neuroinvasiveness of this strain.
Record Date Created: 19920413

8/7/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
07014855 91328036 PMID: 1651044
Neurovirulent strains of herpes simplex virus type 1 are not necessarily competent for reactivatable latency.
Arao Y; Hatano A; Yamada M; Uno F; Nii S
Department of Virology, Okayama University Medical School, Japan.
Acta medica Okayama (JAPAN) Apr 1991, 45 (2) p117-21, ISSN 0386-300X Journal Code: 0417611
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Ability of two neurovirulent strains (F and +GC (LPV) Miyama) of herpes simplex virus type 1 (HSV-1) to establish and maintain reactivatable latency in trigeminal ganglia (TG) was compared after intranasal inoculation of mice. The +GC (LPV) Miyama strain showed a very low rate of virus reactivation in explant cultures of TG, while the F strain showed a high rate of reactivation. These data indicate that neurovirulent strains of HSV-1 are not always competent for reactivatable latency, although most virulent strains of HSV-1 thus far reported were competent for reactivatable latency.
Record Date Created: 19910911

8/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06853228 91157704 PMID: 1981458
Latency competence of herpes simplex virus strains ANG, ANGpath and its gC and gE minus mutans.
Rajcani J; Herget U; Kostal M; Kaerner H C
Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Heidelberg, F.R.G.
Acta virologica. English ed (CZECHOSLOVAKIA) Sep 1990, 34 (5) p477-86, ISSN 0001-723X Journal Code: 0370401
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The latency competence of herpes simplex virus type 1 (HSV-1) strains SC16, KOS, ANG, ANGpath and its mutants ANGpathgC18 (gC minus, spontaneous

point mutation), KOSgC39 (gC minus deletion), ANGpathI2-4 (gE minus deletion), and ANGpathgCI-8 (gE and gC minus double mutan) was compared and DBA/2 mice. While the latent SC16 and KOS reactivated spontaneously in explanted homolateral trigeminal ganglion fragments coming from Velaz DBA/2 mice, methylation inhibitor 5-azacytidine (5-AzaC) was required to achieve reactivation of SC16 in the ganglion explants from Hannover DBA/2 mice. Reactivation of ANGpath in the cultured trigeminal ganglia from both lines of DBA/2 mice occurred only in the presence of the drug. The compound also enhanced the reactivation incidence in the ganglion explants from ANG-infected Hannover DBA/2 mice but not from Velaz DBA/2 mice: in the latter it remained low even in the presence of the inducer. Both gE- mutants failed to establish latency as judged by the failure of reactivation either in the presence or the absence of 5-AzaC. This seemed in accordance with the absence of neural (quick axonal) spread of these mutans in mice (Rajcani et al., 1990). In contrast, both gC- mutans established latency: ANGpathgC18 at an unchanged rate and KOSgC39 at a lower frequency than the parent strain.
Record Date Created: 19910410

8/7/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06711174 91024573 PMID: 2171456
Characterization of glycoprotein C-negative mutants of herpes simplex virus type 1 isolated from a patient with keratitis.
Hidaka Y; Sakuma S; Kumano Y; Minagawa H; Mori R
Department of Virology, School of Medicine, Kyushu University, Fukuoka, Japan.
Archives of virology (AUSTRIA) 1990, 113 (3-4) p195-207, ISSN 0304-8608 Journal Code: 7506870

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recently three strains of herpes simplex virus type 1 (HSV-1), which did not react with Micro Trak Herpes (Syva Co.), were isolated by us from a patient with recurrent herpetic keratitis. In this study we characterized these strains of HSV-1 and found them to be HSV-1 gC- mutants which are very rare isolates from humans. The properties of the HSV-1 strains regarding plaque morphology on Vero cells and chick embryo fibroblasts and viral DNA analysis were the same as those of the usual HSV-1 strains. An immunofluorescence study using anti-gC-1 monoclonal antibody and SDS-PAGE analysis of radiolabeled viral glycoproteins showed that these strains are deficient in gC-1. They were virulent for mice and sensitive to acyclovir and bromovinyldeoxyuridine. Furthermore the infectivity of the strains was inactivated by complement though the phenomenon was not observed in the usual HSV-1 strains. This finding suggests that protection from damages by complement is an important function of gC. In keratitis the effects of complement are thought to be minimal because of the scanty blood supply and this may be the reason why these strains were isolated from the cornea.
Record Date Created: 19901109

8/7/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06196401 89280637 PMID: 2543866
Characterization of encephalitis in adult mice induced by intracerebral inoculation of herpes simplex virus type 1 (KOS) and comparison with mutants showing decreased virulence.
Chrisp C E; Sunstrum J C; Averill D R; Levine M; Glorioso J C
Department of Human Genetics, University of Michigan Medical School, Ann Arbor.
Laboratory investigation; a journal of technical methods and pathology (UNITED STATES) Jun 1989, 60 (6) p822-30, ISSN 0023-6837 Journal Code: 0376617
Contract/Grant No.: AI18228; AI; NIAID; GM34534; GM; NIGMS; RR00200; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The spread of herpes simplex virus type 1 (HSV-1) strain KOS, and two less neurovirulent mutants of the strain was studied in female DBA/2 mice during the 1- to 5-day postinoculation period after intracerebral inoculation. Immunohistopathology showed that wild-type KOS virus first infected the meninges and ependymal cells but did not infect cells at the inoculation sites. The virus continued to spread to some cells directly adjacent to ventricles; however, the most extensive and severe lesions were found in the pyriform lobes and other structures associated with the limbic system. The pattern of spread suggested that direct cell to cell viral spread is important but that retrograde axonal transport to distant sites probably accounts for the more severe lesions associated with the limbic system. Both less neurovirulent mutant viruses multiplied to a much lesser degree in the brain and spread less extensively than the wild type virus when equivalent doses were given; however, when a large dose of the least neurovirulent mar C10.1 mutant virus was inoculated, infection spread rapidly to the same regions of the brain affected by KOS. Studies of mar C10.1 showed that thymidine kinase deficiency, rather than a mutation in the gene coding for glycoprotein C, probably accounted for the decreased neurovirulence of this mutant. This mouse model of HSV-1 virus-induced encephalitis, in combination with appropriate studies of the molecular biology of the HSV-1 KOS strain, should be useful for the study of neurovirulence factors contributing to the pathogenesis of HSV-1.
Record Date Created: 19890721

8/7/18 (Item 18 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
06081728 89156960 PMID: 2537887
Neurovirulence of two clonally related herpes simplex virus type 1 strains in a rabbit seizure model.
Stroop W G; Schaefer D C
Neurovirology Research Laboratory, Veterans Administration Medical Center, Salt Lake City, Utah.
Journal of neuropathology and experimental neurology (UNITED STATES) Mar 1989, 48 (2) p171-83, ISSN 0022-3069 Journal Code: 2985192R
Contract/Grant No.: NS21452; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Herpes simplex virus type 1 (HSV-1) strains vary widely with regard to neurovirulence, but their tropism for specific central nervous system structures and their ability to induce seizures are poorly defined. We have used the clonally related +GC and -GC strains of HSV-1 to define the pathophysiological basis of neurovirulence in a rabbit model. Following intranasal inoculation, +GC infection was nearly uniformly fatal while -GC infection was asymptomatic. The +GC infected animals developed electroencephalographic (EEG) abnormalities which preceded severe motor seizures. Tropism of the +GC strain for specific CNS nerve centers and the expression of viral antigens within them correlated with its virulence. Although both viruses invaded and replicated within the brain, +GC replicated to slightly higher titers and expressed more abundant viral antigen than -GC. The relatively less efficient replication of -GC appeared to correlate with its temperature-sensitive phenotype in vitro. Both +GC and -GC antigens were found in cerebral cortical layers IV-VI, and in several central nervous system trigeminal and olfactory system structures. However, +GC spread more completely throughout the brain to involve the amygdala, nucleus accumbens, several brainstem nuclei and the locus ceruleus. The +GC antigens were also found in cerebral cortical layer I of animals that developed seizures. These results indicate that the ability of HSV-1 to induce electrophysiologic brain abnormalities is associated with its ability to replicate within specific brain nerve centers.
Record Date Created: 19890407

8/7/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
05918944 89021377 PMID: 2845681
Pathogenicity of glycoprotein C negative mutants of herpes simplex virus type 1 for the mouse central nervous system.
Sunstrum J C; Chrisp C E; Levine M; Glorioso J C
Department of Human Genetics, University of Michigan Medical School, Ann Arbor 48109.
Virus research (NETHERLANDS) Aug 1988, 11 (1) p17-32, ISSN 0168-1702 Journal Code: 8410979
Contract/Grant No.: AI18228; AI; NIAID; GM34534; GM; NIGMS; RR00200; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A previous study from our laboratory showed that a mutant of herpes simplex virus type 1 (HSV-1), strain KOS-321, carrying a deletion in the structural gene for glycoprotein C (gC) had reduced pathogenicity for the mouse central nervous system when compared to the wild-type virus (Kumel et al., 1985). In this study, eight additional gC negative (gC-) mutants derived from KOS-321 were shown to vary widely in their ability to induce lethal encephalitis in female DBA/2 mice following intracerebral inoculation. This variation in virulence showed no correlation with thymidine kinase activity. One less virulent gC- strain, gC-39, was further studied to determine whether the neurovirulent phenotype could be restored by rescue of the gC gene using standard marker rescue cotransfection procedures. The resulting progeny contained 2% gC+ recombinant virions and was tested for its ability to cause encephalitis. Although this progeny had increased virulence, it was not attributable to the acquisition of the gC gene since passive immunization of mice with a pool of anti-gC monoclonal antibodies had no effect on the development of encephalitis and only gC- viruses were isolated from diseased brain tissues. In agreement with these findings, individual plaque-purified gC positive (gC+) virus recombinants were shown not to have been restored to the wild-type virus level of neurovirulence. It is concluded that gC is not a virulence determinant in this mouse model of HSV-induced encephalitis and that cotransfection procedures can induce additional mutations that affect viral pathogenesis.
Record Date Created: 19881108

8/7/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
05198707 86268387 PMID: 3015080
In vitro cytopathology and pathogenicity to inbred mice shown by five variants of a laboratory strain of type 1 herpes simplex virus.
Yamada M; Uno F; Nii S
Archives of virology (AUSTRIA) 1986, 90 (3-4) p183-96, ISSN 0304-8608 Journal Code: 7506870
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The in vitro cytopathology and the neurovirulence to inbred mice demonstrated by five variants originally derived from one laboratory strain (Miyama) of type 1 herpes simplex virus (HSV-1) were studied comparatively. Three of the variants are syncytial [+GC (LPV), +GC (SPV), +GC (81)] and

two are non-syncytial [-GCr and -GCf]. The size of plaques produced by the five variants was found to be in the order of +GC (LPV) greater than +GC (81) greater than +GC (SPV) greater than -GCf greater than -GCr. The pathogenicity of these variants was compared in three kinds of inbred mice (AKR, C 3 H/He and C 57 BL) after intraperitoneal (IP) or intracerebral (IC) inoculation. The +GC (LPV) variant was the most virulent as shown by the highest mortality of mice by either route of inoculation. The other four variants caused death of mice only after IC inoculation, and among these variants, +GC (81) was shown to be the most virulent. These data indicate that so far as these five variants of the Miyama strain of HSV-1 are concerned, neurovirulence is positively correlated with their cell fusion activity or the size of plaques which they produce. Pre-IP-inoculation with any of the less virulent variants [-GCr, +GC (SPV) and +GC (81)] protected mice from subsequent lethal infection with +GC (LPV) by the same route of inoculation.
Record Date Created: 19860820

8/7/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
04533348 84216460 PMID: 6328010
Immunogenicity of herpes simplex virus glycoproteins gC and gB and their role in protective immunity.
Glorioso J; Schroder C H; Kumel G; Szczesiul M; Levine M
Journal of virology (UNITED STATES) Jun 1984, 50 (3) p805-12, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: AI 17900; AI; NIAID; AI 18228; AI; NIAID; RR00200; RR ; NCRR; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The relative antigenicity of the individual herpes simplex virus type 1 (KOS) glycoproteins gC and gB was analyzed in BALB/c mice by using KOS mutants altered in their ability to present these antigens on cell surface membranes during infection. The mutants employed were as follows: syn LD70 , a non-temperature-sensitive mutant defective in the synthesis of cell surface membrane gC; tsF13 , a temperature-sensitive mutant defective in the processing of the precursor form of gB to the mature cell surface form at 39 degrees C; and ts606 , an immediate early temperature-sensitive mutant defective in the production of all early and late proteins including the glycoproteins. By comparing the relative susceptibility to immunolysis of mouse 3T3 cells infected at 39 degrees C with wild-type virus, presenting the full complement of the glycoprotein antigens, gC, gB, and gD, with target cells infected with mutants presenting only subsets of these antigens, we determined that a major portion of cytolytic antibody contained in hyperimmune anti-herpes simplex virus type 1 (KOS) mouse antiserum was directed against glycoproteins gC and gB. The relative immunogenicity of wild-type and mutant virus-infected cells also was compared in BALB/c mice. Immunogen lacking the mature form of gB induced a cytolytic antibody titer comparable to that of the wild-type virus, whereas that lacking the mature form of gC showed a 70% reduction in titer. The absence of the mature cell surface forms of gB and gC in immunogen preparations resulted in a 4- to 15-fold reduction in in virus neutralizing titer. Animals immunized with ts606 -infected cells (39 degrees C) induced relatively little virus-specific cytolytic and neutralizing antibody. Analysis of the glycoprotein specificities of these antisera by radioimmunoprecipitation showed that the antigens immunoprecipitated reflected the viral plasma membrane glycoprotein profiles of the immunogens. The absence of the mature forms of gC or gB in the immunizing preparation did not appreciably affect the immunoprecipitating antibody response to other antigens. Mice immunized with wild-type and mutant virus-infected cells were tested for their resistance to intracranial and intraperitoneal challenge with the highly virulent WAL strain of herpes simplex virus type 1. Despite the observed alterations in serum virus-specific antibody induced with the individual immunogens, all animals survived an intraperitoneal challenge of 10 50% lethal doses. However, differences in the survival of animals were obtained upon intracranial challenge.(ABSTRACT TRUNCATED AT 400 WORDS)
Record Date Created: 19840625

8/7/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
03900161 82166339 PMID: 6279513
Initial herpes simplex virus type 1 infection prevents ganglionic superinfection by other strains.
Centifanto-Fitzgerald Y M; Varnell E D; Kaufman H E
Infection and immunity (UNITED STATES) Mar 1982, 35 (3) p1125-32, ISSN 0019-9567 Journal Code: 0246127
Contract/Grant No.: EY02377; EY; NEI; EY02389; EY; NEI; EY02672; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ganglia of rabbits infected with a relatively benign strain of herpesvirus (E-43) and challenged with either of two virulent neurotrophic strains (MP or McKrae) were found to be colonized only by the initial benign infecting strain. Primary infection with the E-43 strain resulted in milder disease when the animals were infected with MP or McKrae strains and also prevented colonization of the ganglion by these strains. Neutralization with anti-glycoprotein C, plaque morphology, cytopathic effects, reconstruction experiments, and restriction endonuclease analysis indicated that the virus recovered from the ganglion was the initial infecting E-43 strain; no traces of the challenging MP and McKrae strains were found. The challenging McKrae strain was shed for several weeks in a

few animals, but the virus isolated from the trigeminal ganglia of these animals was the primary infecting E-43 strain. These results suggest that initial infection with a relatively benign strain of herpesvirus may prevent superinfection of the ganglion (but not necessarily the end organ) by highly virulent herpes simplex virus strains and could have significant implications in the consideration of immunization against this disease in humans.

Record Date Created: 19820614

?t s13/7/1-4 6 7 19

13/7/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13186253 21853715 PMID: 11863417

The complement response against an oncolytic virus is species-specific in its activation pathways.

Wakimoto Hiroaki; Ikeda Keiro; Abe Tatsuya; Ichikawa Tomotsugu; Hochberg Fred H; Ezekowitz R Alan B; Pasternack Mark S; Chiocca E Antonio

Neurosurgery Service and Molecular Neuro-Oncology Laboratories, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, USA.

Molecular therapy : the journal of the American Society of Gene Therapy (United States) Mar 2002, 5 (3) p275-82, ISSN 1525-0016 Journal Code: 100890581

Contract/Grant No.: PO1 CA69246; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A variety of oncolytic viruses (OVs) are being tested in clinical trials for different human cancers. Although the innate immune response is critical as the first line of defense in thwarting viral infection of mammalian cells, little is known of this response in the context of OV therapy of tumors. Investigations of activities against a herpes simplex OV demonstrated that HSV-seronegative sera from rats, mice, and humans efficiently neutralize this OV in vitro. Although this neutralization is due to complement, activation of this innate host defense differs in its pathways among species routinely used in preclinical tumor trials. In rats, both natural immunoglobulins and mannan-binding lectin (MBL) activate complement against the OV, while in mice only MBL is relevant to this activation. However, in humans only natural immunoglobulins play a role in complement activity. Quantitative analyses confirm that in vivo complement depletion facilitates the initial infection of tumors by systemic OVs. Therefore, complement activation against oncolytic HSV vectors proceeds through different pathways in different species. These findings are relevant to preclinical rodent studies of OV therapy and their application to human clinical trials.

Record Date Created: 20020226

13/7/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10687789 20240062 PMID: 10775615

Complement depletion facilitates the infection of multiple brain tumors by an intravascular, replication-conditional herpes simplex virus mutant.

Ikeda K; Wakimoto H; Ichikawa T; Jhung S; Hochberg F H; Louis D N; Chiocca E A

Molecular Neuro-Oncology Laboratories, Neurosurgery Service, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, USA.

Journal of virology (UNITED STATES) May 2000, 74 (10) p4765-75, ISSN 0022-538X Journal Code: 0113724

Contract/Grant No.: CA 69246; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Intravascular routes of administration can provide a means to target gene- and virus-based therapies to multiple tumor foci located within an organ, such as the brain. However, we demonstrate here that rodent plasma inhibits cell transduction by replication-conditional (oncolytic) herpes simplex viruses (HSV), replication-defective HSV, and adenovirus vectors. In vitro depletion of complement with mild heat treatment or in vivo depletion by treatment of athymic rats with cobra venom factor (CVF) partially reverses this effect. Without CVF, inhibition of cell infection by HSV is observed at plasma dilution as high as 1:32, while plasma from CVF-treated animals displays anti-HSV activity at lower dilutions (1:8). When applied to the therapy of intracerebral brain tumors, in vivo complement depletion facilitates the initial infection (assayed at the 2-day time point) by an intra-arterial replication-conditional HSV of tumor cells, located within three separate and distinct human glioma masses. However, at the 4-day time point, no propagation of HSV from initially infected tumor cells could be observed. Previously, we have shown that the immunosuppressive agent, cyclophosphamide (CPA), facilitates the in vivo propagation of an oncolytic HSV, delivered intravascularly, within infected multiple intracerebral masses, by inhibition of both innate and elicited anti-HSV neutralizing antibody response (K. Ikeda et al., Nat. Med. 5:881-889, 1999). In this study, we thus show that the addition of CPA to the CVF treatment results in a significant increase in viral propagation within infected tumors, measured at the 4-day time period. The concerted action of CVF and CPA significantly increases the life span of athymic rodents harboring three separate and large glioma xenografts after treatment with intravascular, oncolytic HSV. Southern analysis of viral genomes analyzed by PCR reveals the presence of the oncolytic virus in the brains, livers, spleens, kidneys, and intestine of treated animals, although none of these tissues displays evidence of HSV-mediated gene expression. In light of clinical trials of oncolytic HSV for malignant

brain tumors, these findings suggest that antitumor efficacy may be limited by the host innate and elicited humoral responses.
Record Date Created: 20000511

13/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10366616 99353353 PMID: 10426310
Oncolytic virus therapy of multiple tumors in the brain requires suppression of innate and elicited antiviral responses.
Ikeda K; Ichikawa T; Wakimoto H; Silver J S; Deisboeck T S; Finkelstein D ; Harsh G R; Louis D N; Bartus R T; Hochberg F H; Chiocca E A
Molecular Neuro-Oncology Laboratories, Neurosurgery Service, Massachusetts General Hospital, Harvard Medical School, Charlestown 02129, USA.
Nature medicine (UNITED STATES) Aug 1999, 5 (8) p881-7, ISSN 1078-8956 Journal Code: 9502015
Contract/Grant No.: P01 CA 69246; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The occurrence of multiple tumors in an organ heralds a rapidly fatal course. Although intravascular administration may deliver oncolytic viruses/vectors to each of these tumors, its efficiency is impeded by an antiviral activity present in complement-depleted plasma of rodents and humans. Here, this activity was shown to interact with complement in a calcium-dependent fashion, and antibody neutralization studies indicated preimmune IgM has a contributing role. Short-term exposure to cyclophosphamide (CPA) partially suppressed this activity in rodents and humans. At longer time points, cyclophosphamide also abrogated neutralizing antibody responses. Cyclophosphamide treatment of rats with large single or multiple intracerebral tumors substantially increased viral survival and propagation, leading to neoplastic regression.
Record Date Created: 19990826

13/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10205091 99176846 PMID: 10078960
Complementary adenoviral vectors for oncolysis.
Alemany R; Lai S; Lou Y C; Jan H Y; Fang X; Zhang W W
Gene Therapy Program, University of Alabama, Birmingham 35294, USA.
Cancer gene therapy (UNITED STATES) Jan-Feb 1999, 6 (1) p21-5, ISSN 0929-1903 Journal Code: 9432230
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Replication-competent adenoviruses (Ads) were used for oncolytic virotherapy soon after they were discovered. Recently mutated and genetically engineered Ads have been shown to selectively lyse tumor cells. We have split the human Ad type 5 genome into two defective viruses that complement each other only in certain tumor cells. The genome of one of these vectors, GT5610, contains only the minimal viral elements required in cis for replication and packaging and the E1 viral genes with E1A under the control of the human alpha-fetoprotein promoter. This "controlled" vector has a capacity for 30 kilobases of foreign DNA. The supplemental vector, AdHbeta, contains all adenoviral genes except for E1. Both vectors were designed to carry heterologous reporter genes whose expression could be detected throughout the tumor. Coinfection of hepatocarcinoma cells that have the capacity to transcribe genes under the control of the alpha-fetoprotein promoter leads to cell lysis and copropagation. The oncolytic spread of these complementary vectors in vivo was demonstrated by the intratumoral injection of human hepatocarcinomas xenografted in severe combined immunodeficient (SCID) mice. This system presents safety and gene capacity features that could yield a therapeutic advantage over oncolysis by a single virus.
Record Date Created: 19990526

13/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06985285 91298361 PMID: 2069169
Generation of cytotoxic NK cells in peripheral blood and bone marrow of patients with acute myelogenous leukemia after continuous infusion with recombinant interleukin-2.
Lotzova E; Savary C A; Schachner J R; Huh J O; McCredie K
Department of General Surgery, University of Texas, M.D. Anderson Cancer Center, Houston 77030.
American journal of hematology (UNITED STATES) Jun 1991, 37 (2) p88-99, ISSN 0361-8609 Journal Code: 7610369
Contract/Grant No.: CA 39632; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have studied the cytotoxic profile and distribution of lymphocyte subsets of patients with acute myelogenous leukemia in second remission, after continuous infusion with recombinant interleukin-2 (IL-2). The patients received repetitive cycles of 1-1.25 x 10(6) U/m2/day of IL-2, given as 4 days continuous intravenous infusion followed by a 3-day treatment-free interval for the first 4 weeks. Patients receiving greater than 4 cycles were treated with the same dose of IL-2 continuously for 4 days, followed by a 10-day treatment-free interval. These studies showed that IL-2 treatment resulted in the generation of peripheral blood cytotoxic activity against both NK-susceptible, K-562, and NK-resistant

Daudi cell lines. In most patients, enhancement of lytic activity increased with the number of IL-2 infusions. The cytotoxicity in some patients increased as much as 700-fold and 830-fold against K-562 and Daudi cells, respectively. It is of importance that oncolytic activity was also induced in bone marrow compartment (up to 182-fold against K-562). Some decline in cytotoxicity was observed within 14 days after initiation of IL-2 infusion in peripheral blood, but high levels of lytic activity persisted at this time in bone marrow. It is of interest to note that the cytotoxicity of in vivo IL-2 primed lymphocytes was further potentiated by IL-2 in vitro. Importantly, the cytotoxic cells induced in vitro displayed lytic activity against fresh leukemic blasts. Phenotypic analysis demonstrated that CD3-, CD56+ NK cells were significantly increased by in vivo IL-2 treatment (34 to 47-fold in absolute numbers), while CD3-, CD56+ T-cell subset remained low. Characterization of cytotoxic cells using the complement-dependent assay and monoclonal antibodies indicated that both the in vivo-induced and ex vivo-potentiated lytic function was mediated by CD3-, CD56+, CD16- -NK cells.

Record Date Created: 19910813

13/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06920632 91232249 PMID: 2030606

Highly oncolytic adherent lymphocytes: therapeutic relevance for leukemia.

Lotzova E; Savary C A; Totpal K; Schachner J; Lichtiger B; McCredie K B; Freireich E J

Department of General Surgery, University of Texas, M.D. Anderson Cancer Center, Houston 77030.

Leukemia research (ENGLAND) 1991, 15 (4) p245-54, ISSN 0145-2126 Journal Code: 7706787

Contract/Grant No.: CA 39632; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have generated and characterized a highly oncolytic adherent lymphocyte subset (A-LAK) from eight leukemic patients with non-lymphocytic leukemia (NLL) in remission and one NLL patient in relapse. Our studies demonstrated that A-LAK was superior in its oncolytic activity (tested in a 3-h 51Cr release assay) to conventionally prepared (LAK) and non-adherent (NA) IL-2 cultures. No activity was observed by this highly oncolytic subset against normal bone marrow (BM). A-LAK also displayed highest proliferative activity in 7-11 day cultures (5- to 58-fold expansion) in comparison to LAK (0.7- to 2.7-fold) or NA (1.0- to 2.6-fold) cultures. Analysis of phenotype of unseparated, NA and adherent (A-LAK) lymphocytes 24 h after IL-2 activation showed that the A-LAK was composed predominantly of high intensity (bright) CD11a+ (LFA-1) lymphocytes (75 +/- 4.8%) when compared to the other two populations (12 +/- 2.1%). Similarly, A-LAK contained higher proportion of CD11b (CR3 receptor)-positive lymphocytes (39 +/- 2.1%) than unseparated and NA lymphocytes (11 +/- 1.4%). Double marker phenotypic studies showed that A-LAK cultures were heterogeneous and distribution of individual lymphocyte subsets differed among NLL patients. While in A-LAK culture of some patients the CD56+, CD3- natural killer (NK) cell subset was predominant, CD3+, CD56- lymphocyte subset was prevalent in others. Highest A-LAK lytic activity was always correlated with highest NK cell content. Characterization studies (using the complement-depletion technique) showed that independently of the distribution of lymphocytes in A-LAK cultures, CD16+, CD56+, CD3- NK cell subset displayed highest oncolytic effect. CD5+ subset also participated in cytotoxic function. These observations indicated that A-LAK may represent a new therapeutic approach to treatment of leukemia.

Record Date Created: 19910618

13/7/19 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0137088 DBA Accession No.: 92-09580 PATENT
Selective killing of neoplastic cells - herpes simplex virus thymidine-kinase-negative mutant may be used in astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, ependymoma, etc. tumor therapy

PATENT ASSIGNEE: Gen.Hosp.Boston; Harvard-College 1992
PATENT NUMBER: CA 2051289 PATENT DATE: 920315 WPI ACCESSION NO.: 92-175671 (9222)
PRIORITY APPLIC. NO.: US 582057 APPLIC. DATE: 900914
NATIONAL APPLIC. NO.: CA 51289 APPLIC. DATE: 910913
LANGUAGE: English

ABSTRACT: A method is claimed for selectively killing tumor cells which involves infecting the cells with an altered virus which is capable of replication in tumor cells but not in normal cells. The altered virus may be a mutated virus such as a herpes simplex virus thymidine-kinase (EC-2.7.1.21) mutant, e.g. HSV-1-dlsptk. The altered virus contains heterologous promoters, which are used to express proteins necessary for viral replication, and are selectively capable of expression in tumor cells. The viral infection leads to the destruction of the tumor cells by oncolysis and/or xenogenization without causing systemic viral infection. The method involves mutating one of the viral genes, encoding thymidine-kinase, in herpes simplex virus. This mutant virus is then used to treat the tumor. This is accomplished by the virus's ability to replicate within the malignant glioma cells, using the tumor cell's endogenous thymidine-kinase activity to complement the mutation, and leading to lysis of the tumor cell. The method is used especially for treating nervous system tumors e.g. astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, etc. (37pp)

?t s19/7/17 7 8 11 20 22 50 57

19/7/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
07102311 92036712 PMID: 1657543

Lysis of herpes simplex virus-infected cells by lymphokine-activated killer cells.

Chu C T; Lee P; Lin B J; Sun M J; Hsieh K H

Department of Bacteriology and Pediatrics, National Taiwan University, College of Medicine, Taipei, Republic of China.

Zhonghua min guo wei sheng wu ji mian yi xue za zhi = Chinese journal of microbiology and immunology (TAIWAN) Feb 1991, 24 (1) p108-18, ISSN 0253-2662 Journal Code: 8008067

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Activation of human peripheral blood mononuclear cells (PBMC) or murine splenocytes with recombinant interleukin-2 (rIL-2) has been found to be able to generate cells which are lytic in vitro for a variety of cells infected by herpes simplex virus (HSV). Lymphokine-activated killer (LAK) cells were generated by the incubation of human PBMC or murine splenocytes with 500 u/ml of rIL-2 for 3 to 4 days in a CO2 incubator at 37 degrees C. These cells were lytic to cultured tumor cell lines, yet sparing normal primary cell cultures as has been reported. Human PBMC infected with HSV, however, were susceptible to the lytic effect of these LAK cells. From 30 to 50 percent lysis of HSV-infected human PBMC was observed when the effector-to-target ratios were 40:1 and 100:1 respectively by four hr 51Cr-release assays. Similar cytolytic effect was observed when mouse embryonic fibroblasts (MEF) were infected with HSV and used as targets when rIL-2-activated mouse splenocytes were used as effectors. The cytolytic effects of LAK cells on the HSV-infected cells can be demonstrated even after lowering of NK activities by the treatment of effector cells with anti-NK antibody Leu-11b plus complement. Cytolytic effects were not restricted to the autologous system, and could be demonstrated in the heterologous system as well. Human LAK cells killed not only HSV-infected autologous PBMC but also infected mouse embryonic fibroblasts. However, mouse LAK cells exhibit species-specific cytotoxicity. In conclusion, it was demonstrated that LAK cells are cytolytic to HSV-infected cells in both human and murine systems.

Record Date Created: 19911211

19/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10141677 99114733 PMID: 9918201

Interleukin-6 modulated conditionally replicative adenovirus as an antitumor/cytotoxic agent for cancer therapy.

Rancourt C; Piche A; Gomez-Navarro J; Wang M; Alvarez R D; Siegal G P; Fuller G M; Jones S A; Curiel D T

Gene Therapy Program, University of Alabama at Birmingham, 35294, USA.

Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jan 1999, 5 (1) p43-50 , ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: RO1 CA68245; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In this study, we report that an interleukin-6 (IL-6)-inducible E1A-substituting activity can be exploited for the production of infectious adenoviral particles during infection with the E1A-deleted adenovirus (Ad) Ad5dl312. The basal level of complementation can be increased by 1.5 log by induction of the HepG2 cells with recombinant human IL-6. Additionally, the IL-6-inducible E1A-substituting activity can complement E1A deletion in other cancer cell lines to render them Ad producer cells on induction with recombinant human IL-6, although the efficiency of complementation varies between cell lines. Ad5dl312 can replicate in, produce cytotoxic effect, and kill human tumor cells without addition of exogenous IL-6 in the context of tumor cells possessing an IL-6 autocrine arc, such as ovarian tumor cells. In contrast, normal human mesothelial cells isolated from normal human peritoneum lining do not support replication of Ad5dl312, even in the presence of exogenous IL-6. These results suggest that Ad5dl312 could be used as a cytotoxic agent to selectively kill tumor cells responsive to or possessing an IL-6 autocrine arc.

Record Date Created: 19990324

19/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
10066170 99053290 PMID: 9839555

Antigenic and immunological mimicry of peptide mimotopes of Lewis carbohydrate antigens.

Luo P; Agadjanyan M; Qiu J; Westerink M A; Steplewski Z; Kieber-Emmons T

Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.

Molecular immunology (ENGLAND) Sep 1998, 35 (13) p865-79, ISSN 0161-5890 Journal Code: 7905289

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Peptides may substitute for carbohydrates in reactions with carbohydrate-specific molecules. Recently, we found that peptides containing aromatic residues mimic mucin and histo-blood group related carbohydrate epitopes, eliciting polyclonal responses cross-reactive with bacterial and viral antigens that express these carbohydrate forms. These

results demonstrate that peptides can function in in vivo and in vitro models as carbohydrate surrogate antigens. To further explore the nature of the antigenic and immunogenic properties of such mimotopes, synthetic peptides with aromatic amino acids were tested to delineate reactivity patterns with several anti-neolactoseries monoclonal antibodies (MAbs). These MAbs recognize biologically important conformations of the histo-blood group related Lewis antigens expressed on the surface of a variety of human cancers. Results by ELISA demonstrate that the MAbs can distinguish particular peptide motifs that include the sequences GGIYYPYDIYYPYDIYYPYD, GGIYWRYDIYWRYDIYWRYD and GGIYYRYDIYYRYDIYYRYD.
Substitution of Arg by Pro diminished the reactivity of the anti-Lewis Y (LeY) MAb BR55-2. Binding of LeY to BR55-2 was inhibitable by the Arg containing peptides. Serum against all three peptides displayed reactivity with synthetic histo-blood group related antigen probes. Immunologic presentation of the peptides as multiple antigen peptides (MAPs) improved peptide ability to induce LeY specific immune responses. Serum bound to human tumor cells that preferentially expressed neolactoseries antigens, but not to normal tissues. Immunoprecipitation of human breast tumor cell lysates before and after treatment with tunicamycin confirmed serum carbohydrate binding. The anti-peptide sera mediated tumor cell killing by complement mediated cytotoxicity. These results indicate that mapping peptide epitopes with anti-carbohydrate antibodies can lend to defining antibody fine specificities that can go undetected by screening of carbohydrate antigens alone. In addition, these results confirm that peptides and carbohydrates can bind to the same antibody binding site and that peptides can structurally mimic salient features of carbohydrate epitopes.
Record Date Created: 19981214

19/7/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09379611 97284439 PMID: 9139853
Generation of an anti-tumour immune response in a non-immunogenic tumour: HSVtk killing in vivo stimulates a mononuclear cell infiltrate and a Th1-like profile of intratumoural cytokine expression.
Vile R G; Castleden S; Marshall J; Camplejohn R; Upton C; Chong H
Imperial Cancer Research Fund Laboratory of Cancer Gene Therapy, London, UK. vile@europa.lif.icnet.uk
International journal of cancer. Journal international du cancer (UNITED STATES) Apr 10 1997, 71 (2) p267-74, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Direct delivery of the herpes simplex virus thymidine kinase (HSVtk) gene, in combination with the prodrug ganciclovir (GC), has been used for the treatment of localised, inoperable tumours. Several groups have shown that when rodent tumours are ablated in vivo with suicide genes, anti-tumour immunity can also be generated. Hence, this approach may also be useful in treating disseminated disease. Here we have studied the mechanisms associated with this anti-tumour immunity. In B16 HSVtk+ tumours being killed in vivo with GC treatment, we observed the induction of a pronounced intratumoural infiltrate of macrophages, CD4+ and CD8+ T cells. In addition, using reverse transcriptase polymerase chain reaction, expression of interleukin (IL)-2, IL-12, interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha) and granulocyte/macrophage colony-stimulating factor (GM-CSF) but not IL-4, IL-6 or IL-10, was observed, a profile of cytokine expression which resembles that of a Th1 immune response. To complement these findings, we also investigated the mechanisms by which expression of HSVtk leads to cell death. Our data show that B16/HSVtk+ cells die predominantly by necrosis, rather than apoptosis, on exposure to GC, a process which may be associated with the generation of anti-tumour inflammatory responses. From these data we propose a model for the induction of anti-tumour immunity using suicide genes and discuss the development of improved vectors for gene therapy to augment these effects in vivo.
Record Date Created: 19970523

19/7/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06258078 89343948 PMID: 2548078
Use of a glucocorticoid-inducible promoter for expression of herpes simplex virus type 1 glycoprotein gC1, a cytotoxic protein in mammalian cells.
Friedman H M; Yee A; Diggelmann H; Hastings J C; Tal-Singer R; Seidel-Dugan C A; Eisenberg R J; Cohen G H
Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.
Molecular and cellular biology (UNITED STATES) Jun 1989, 9 (6) p2303-14, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: AI-18289; AI; NIAID; FO6 TWO1162; TW; FIC; HL 28220; HL; NHLBI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Abundant expression of herpes simplex virus type 1 glycoprotein gC (gC1) in transfected mammalian cells has not previously been achieved, possibly because gC1 protein is toxic to cells. To approach this problem, the gC1 coding sequence was placed under the control of the weak but inducible glucocorticoid-responsive promoter from the mouse mammary tumor virus (MMTV) long terminal repeat (LTR). As controls to evaluate for gC1

cytotoxicity, the MMTV LTR promoter was used to express glycoprotein gD1, and a strong, constitutive promoter from the Moloney murine sarcoma virus LTR was used to express gC1. L cells were transfected with these constructs, and a clone expressing gC1 from the inducible MMTV LTR promoter was analyzed. In the absence of glucocorticoid (dexamethasone) stimulation, only a low level of gC1 mRNA expression was detected; after overnight stimulation with dexamethasone, transcription increased approximately 200-fold. Abundant gC1 protein that was functionally active in that it bound complement component C3b, was produced. From passages 5 through 26 (70 cell population doublings), the gC1-producing clone became less responsive to overnight dexamethasone stimulation. The block to gC1 expression occurred at the level of transcription and was associated with hypermethylation of the MMTV LTR DNA. Treatment of the clone with 5-aza-2'-deoxycytidine partially reversed the block in gC1 protein production. Late-passage cells assumed a gC1-negative phenotype that appeared to offer a selective growth advantage, which suggested that gC1 was cytotoxic. Several findings support this view: (i) some cells expressing gC1 after overnight stimulation with dexamethasone assumed bizarre, syncytial shapes; (ii) continuous stimulation with dexamethasone for 5 weeks resulted in death of most cells; (iii) cells transfected with gC1 under the control of the strong Moloney murine sarcoma virus promoter assumed bizarre shapes, and stable gC1-expressing clones could not be established; and (iv) cells induced to express gD1 retained a normal appearance after overnight stimulation or 15 weeks of continuous stimulation with dexamethasone. The inducible MMTV LTR promoter is useful for expressing gC1 and may have applications for expressing other cytotoxic proteins.

Record Date Created: 19890921

19/7/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
06056474 89135917 PMID: 2783887

Factors influencing antibody-mediated cytotoxicity during the immunotherapy of Rauscher-virus-induced myeloid leukemic cells.

Berends D; van der Kwast T H; de Both N J; Mulder P G

Department of Pathology, Erasmus University Rotterdam, The Netherlands.

Cancer immunology, immunotherapy : CII (GERMANY, WEST) 1989, 28 (2) p123-30, ISSN 0340-7004 Journal Code: 8605732

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The present study was undertaken to determine the factors that influence antibody-mediated cytotoxicity during immunotherapy of virally transformed tumor cells. As model a Rauscher-virus-induced myeloid leukemic cell line of BALB/c origin (RMB-1) was used, which forms disseminated tumors, when inoculated intravenously in BALB/c mice. As previously reported, prolonged survival was obtained when tumor-bearing mice were treated in vivo with a single high dose of a tumor-specific IgG2a monoclonal antibody. This study shows that antibody-dependent cellular cytotoxicity is an important mechanism involved in tumor cell destruction. Since in vitro studies showed that peritoneal macrophages were capable of killing RMB-1 cells in the presence of tumor-specific monoclonal antibody and since in the tumors of mice treated with monoclonal antibody a high influx of macrophages was observed histologically, it is likely that macrophages play an important effector role in elimination of tumor cells. Successful therapy in C5-complement-deficient tumor-bearing mice suggests that complement-dependent cytotoxicity does not play a major role. In nude (T-cell-deficient) mice the therapeutic effect of tumor-specific IgG2a antibody was significantly less than in immunocompetent mice. Although infiltration analysis of tumors of treated and untreated mice showed equally low numbers of helper-T and suppressor/cytotoxic T-cells, the mortality studies of T-cell-deficient and immunocompetent mice indicate that T-cells play a substantial, auxiliary role during antibody-mediated, tumor destruction in our model.

Record Date Created: 19890403

19/7/50 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0245245 DBA Accession No.: 1999-15346 PATENT

New virus useful for killing specific tumor cells - gene therapy vector for tumor therapy

AUTHOR: Parks G D

CORPORATE SOURCE: Winston-Salem, NC, USA.

PATENT ASSIGNEE: Univ.Wake-Forest 1999

PATENT NUMBER: WO 9946278 PATENT DATE: 19990916 WPI ACCESSION NO.:
1999-561657 (1947)

PRIORITY APPLIC. NO.: US 41987 APPLIC. DATE: 19980313

NATIONAL APPLIC. NO.: WO 99US5388 APPLIC. DATE: 19990312

LANGUAGE: English

ABSTRACT: A composition of a simian virus-5 (SV5) vector (I) having a lipid membrane and genome including a hemagglutinin-neuraminidase (HN) gene region is claimed. (I) does not express an integral membrane bound HN protein on the surface of the lipid membrane and includes a sequence encoding a membrane bound protein having an extracellular part, able to bind a target other than sialic acid. Also claimed are: a recombinant nucleic acid (NA) comprising an SV5 genome which does not express active HN and comprises the coding sequence for a fusion of the cytoplasmic and membrane spanning regions of a SV5 membrane protein and a foreign extracellular cell targeting protein region; the full-length complement of the NA; preparation of (I) by obtaining a plasmid containing a DNA copy of a SV5 genome, deleting part of the HN gene,

inserting NA encoding a fusion of the SV5 F protein C-terminal and membrane spanning regions fused to a single chain antibody, transferring the plasmid to a cell, transferring the helper plasmids that express virus replication proteins to the cell, generating 3' ends of the DNA and recovering (I); and a composition of the NA. (I) is used for tumor gene therapy. (25pp)

19/7/57 (Item 10 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0137088 DBA Accession No.: 92-09580 PATENT
Selective killing of neoplastic cells - herpes simplex virus thymidine-kinase-negative mutant may be used in astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, ependymoma, etc. tumor therapy
PATENT ASSIGNEE: Gen.Hosp.Boston; Harvard-College 1992
PATENT NUMBER: CA 2051289 PATENT DATE: 920315 WPI ACCESSION NO.: 92-175671 (9222)
PRIORITY APPLIC. NO.: US 582057 APPLIC. DATE: 900914
NATIONAL APPLIC. NO.: CA 51289 APPLIC. DATE: 910913
LANGUAGE: English
ABSTRACT: A method is claimed for selectively killing tumor cells which involves infecting the cells with an altered virus which is capable of replication in tumor cells but not in normal cells. The altered virus may be a mutated virus such as a herpes simplex virus thymidine-kinase (EC-2.7.1.21) mutant, e.g. HSV-1-dlsptk. The altered virus contains heterologous promoters, which are used to express proteins necessary for viral replication, and are selectively capable of expression in tumor cells. The viral infection leads to the destruction of the tumor cells by oncolysis and/or xenogenization without causing systemic viral infection. The method involves mutating one of the viral genes, encoding thymidine-kinase, in herpes simplex virus. This mutant virus is then used to treat the tumor. This is accomplished by the virus's ability to replicate within the malignant glioma cells, using the tumor cell's endogenous thymidine-kinase activity to complement the mutation, and leading to lysis of the tumor cell. The method is used especially for treating nervous system tumors e.g. astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, etc. (37pp)
? t s23/7/9 15 23
23/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
05096315 86169711 PMID: 2420891
Enhanced lysis of herpes simplex virus type 1-infected mouse cell lines by NC and NK effectors.
Colmenares C; Lopez C
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) May 1 1986, 136 (9) p3473-80, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: CA 08748; CA; NCI; CA 23766; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Spontaneously cytotoxic murine lymphocytes lysed certain cell types infected by herpes simplex virus type 1 (HSV-1) better than uninfected cells. The levels of virus-directed lysis varied widely from target to target, and we found that differences in virus-directed lytic efficiency could be attributed both to the characteristics of HSV-1 replication in the different targets and to the subgroup of natural effector cells which mediated lysis. Although HSV-1 adsorbed to the surface of all the target cells, those in which the virus replicated more efficiently were lysed to a greater extent. As targets, we used cell lines that, when uninfected, were spontaneously lysed by NK cells (YAC-1) or by NC cells (WEHI-164). We also used a fibroblastoid cell line (M50) and a monocytic tumor line (PU51R), which were not spontaneously killed. Using complement-mediated elimination of Qa-5-positive or asialo-GM1-positive NK cells to distinguish NK from NC activity, we found that NK cells lysed HSV-1-infected YAC cells better than uninfected cells, and an NC-like activity selectively lysed HSV-1-infected WEHI cells. In addition, we showed that both NK and NC cytotoxicities contributed to the lysis against the HSV-1-infected fibroblastoid line, M50, but the infected PU51R cells were killed by only NK effectors. These findings were consistent with the results of experiments performed to define the role of interferon in induction of virus-augmented cytolysis. Increased lysis of YAC-HSV and PU51R-HSV was entirely due to interferon activation and was completely abolished by performing the 51Cr-release assay in the presence of anti-interferon serum. Because NC activity was not augmented by interferon, virus-enhanced NC lysis of M50-HSV and WEHI-HSV was not due to this nonspecific mechanism. Together, our data show that HSV-1 infection of NK/NC targets induces increased cytotoxicity, but the effector cell responsible for lysis is determined by the uninfected target, or by an interaction between the virus and target cell, rather than by a viral determinant alone.
Record Date Created: 19860522

23/7/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
03661318 81214230 PMID: 6165679
Function, target-cell preference and cell-surface characteristics of herpes-simplex virus type-2-induced non-antigen-specific killer cells.
Armerding D; Simon M M; Hammerling U; Hammerling G J; Rossiter H
Immunobiology (GERMANY, WEST) 1981, 158 (4) p347-68, ISSN 0171-2985 Journal Code: 8002742
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed

Wild-type and congenitally athymic nude mice injected with herpes-simplex virus type 2 (HSV 2) responded with a local outburst of non-antigen-specific killer cells masking any virus-specific response. Cytolytic activity could be assayed on mouse-tumor cell lines and on syngeneic or allogeneic non-transformed cells from various sources. Some of the tumor cell lines and proteose-peptone-induced peritoneal exudate cells were lysed more efficiently after infection with either HSV 2, vaccinia or influenza A virus. Preference for virus-infected target cells was already expressed 24 hours after HSV-2 injection. Killing activity was not H-2-restricted, not complement- or immunoglobulin-dependent and did not involve Fc receptors. The cytotoxic cells were non-adherent and could be shown to express Thy1, Quat4, and Quat4 cell-surface antigens. They lacked immunoglobulin and Lyt1: Lyt2,3 determinants. The functional and serological characteristics identify the HSV-2-induced cytolytic cells as natural killer (NK) cells. The potential importance of this cell population for natural resistance will be discussed.

Record Date Created: 19810810

23/7/23 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0235485 DBA Accession No.: 99-05586 PATENT
Selectively targeting and killing tumor cells - adeno virus or retro virus vector-mediated mouse alpha-1,3-galactosyltransferase gene transfer and expression in tumor cell: antibody administration for complement-mediated tumor cell lysis
AUTHOR: Link Jr C J; Levy J P
CORPORATE SOURCE: Des Moines, IA, USA.
PATENT ASSIGNEE: Hum.Gene-Ther.Res.Inst.Des-Moines 1999
PATENT NUMBER: US 5869035 PATENT DATE: 990209 WPI ACCESSION NO.: 99-152690 (9913)
PRIORITY APPLIC. NO.: US 748344 APPLIC. DATE: 961113
NATIONAL APPLIC. NO.: US 748344 APPLIC. DATE: 961113
LANGUAGE: English
ABSTRACT: A new method of selectively targeting and killing tumor cells involves transforming the tumor cells with a DNA sequence controlled by a tetracycline-controlled transactivator responsive promoter, creating a galactosyl epitope, and contacting tumor with human serum to induce complement-mediated cell destruction. Also claimed is a method for targeting and killing tumor cells which involves: transducing the tumor cells with a recombinant adeno virus or retro virus vector containing the DNA, where expression of the protein creates a galactosyl epitope; and exposing the transformed tumor cells to human serum so that the cells can be killed by complement-mediated cell lysis. The DNA preferably encodes mouse alpha-1,3-galactosyltransferase and the DNA may be a mini-viral herpes simplex virus plasmid vector. The vector contains a replication origin from herpes simplex virus, a herpes simplex virus packaging sequence, an Epstein-Barr virus latent replication origin and a transcription unit sequence encoding an alpha-1,3-galactosyltransferase. The transcription unit is a promoter inducible for doxycycline. (24pp)

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$7.14 151 Types
$26.52 Estimated cost File155
$6.81 0.399 DialUnits File357
$0.00 16 Type(s) in Format 6
$10.80 4 Type(s) in Format 7
$10.80 20 Types
$17.61 Estimated cost File357
OneSearch, 2 files, 6.455 DialUnits FileOS
$6.93 TELNET
$51.06 Estimated cost this search
$51.39 Estimated total session cost 6.545 DialUnits
Logoff: level 02.05.22 D 08:04:34